Original Article

Stereotactic body radiotherapy for locally-advanced unresectable pancreatic cancer—patterns of care and overall survival

Michael J. Dohopolski[1], Scott M. Glaser[2], John A. Vargo[2], Goundappa K. Balasubramani[3], Sushil Beriwal[2]

[1]Department of Radiation Oncology, University Pittsburgh School of Medicine, Pittsburgh, PA, USA; [2]Department of Radiation Oncology, University of Pittsburgh Cancer Institute, Pittsburgh, PA, USA; [3]Department of Epidemiology, School of Public Health, University of Pittsburgh, Pittsburgh, PA, USA

Contributions: (I) Conception and design: SM Glaser, S Beriwal; (II) Administrative support: SM Glaser, S Beriwal; (III) Provision of study materials or patients: SM Glaser, JA Vargo, MJ Dohopolski, GK Balasubramani; (IV) Collection and assembly of data: SM Glaser, JA Vargo, MJ Dohopolski, GK Balasubramani; (V) Data analysis and interpretation: SM Glaser, JA Vargo, MJ Dohopolski, GK Balasubramani; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Sushil Beriwal, MD. Magee Womens Hospital of UPMC (Radiation-Oncology), 300 Halket St., Pittsburgh, PA 15213, USA. Email: beriwals@upmc.edu.

Background: Unresectable pancreatic cancer remains a challenging disease to treat. Stereotactic body radiotherapy (SBRT) allows for a higher biologically equivalent dose in an abbreviated course more convenient for patients and the integration of systemic therapy. We sought to investigate utilization trends and survival outcomes for patients treated with pancreatic SBRT versus conventionally fractionated radiotherapy (CFRT).

Methods: We engaged the National Cancer Database (NCDB) from 1998–2012 and identified locally-advanced unresectable patients with histologically confirmed, non-metastatic, pancreatic adenocarcinoma who received radiotherapy. Patients who received CFRT (1.5–4.0 Gy per fraction to a dose of ≥45 Gy, n=11,879) were compared to those who received SBRT (6–15 Gy per fraction to a dose of ≥20 Gy, n=474).

Results: Median follow-up was 11.0 months (18.4 months for survivors). SBRT utilization increased from 0.2% to 7.4% from 1998 to 2012 (P<0.05). On multivariable analysis, factors predictive for preferential utilization of SBRT over CFRT were later year of diagnosis, age ≥75 years, increased facility volume, and no chemotherapy in the initial treatment plan. Unadjusted median survival was 11.2 months for CFRT *vs.* 12.6 months for SBRT (P=0.002). Results were consistent in the propensity matched model. Variables predictive for improved survival on multivariable analysis were diagnosis after 2010, younger age, lower comorbidity score, tumor size <3 cm, nodal stage zero, and receipt of chemotherapy (P<0.05).

Conclusions: SBRT utilization has increased significantly and is associated with a small absolute improvement in overall survival (OS) compared to CFRT. The decreased treatment time, without apparent compromise in survival, makes SBRT an attractive option for patients with unresectable pancreatic cancer warranting further research.

Keywords: Pancreatic cancer; stereotactic body radiotherapy (SBRT); patterns of care; survival

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Introduction

A majority of non-metastatic pancreatic cancer patients present with unresectable disease, ultimately limiting their 5-year survival to approximately 7% (1). Treatment at this stage usually includes chemotherapy and/or radiation therapy. The role of conventionally fractionated radiotherapy (CFRT) is controversial, however, as several studies have published contradictory results regarding its efficacy when combined with chemotherapy compared to chemotherapy alone (2-4). While a more recent trial, LAP07, did not demonstrate a statistically significant difference in median survival between the two, it did demonstrate that a significant portion of individuals experienced locoregional progression. It also illustrated the potential improvements in quality of life afforded by the addition of radiotherapy through the delayed and/or decreased need for salvage therapies (4). These results not only encourage the need for improved systemic treatments but local therapies as well.

These local therapies, however, must have tolerable toxicity profiles. Many studies have commented on the relatively low potential benefit of CFRT in relation to the increased toxicity (2,5). Thus other modalities of radiation therapy, such as stereotactic body radiation therapy (SBRT), with potentially more favorable toxicity profiles warrant further investigation (6). SBRT allows for a higher biologically equivalent dose to be delivered both with more conformality and in a shorter period of time, potentially widening the therapeutic ratio, increasing patient convenience, and minimizing interruptions in systemic therapy.

Use of SBRT for the treatment of pancreatic cancer is not novel as reports establishing its feasibility were published in the early 2000's (7-10). However, early adoption was limited by concerns of bowel toxicity due to a lack of awareness of the sensitivity of the adjacent duodenum to high dose per fraction (up to 25 Gy in 1 fraction) and larger margins used in initial experiences (8,10,11). With increased awareness of the importance of duodenal dose and incorporation of fractionation over 3–5 fractions, multiple single-institutional series and prospective phase 1–2 studies have more recently demonstrated favorable local control (LC) and toxicity profiles (6,9,12). Thus, we hypothesize that the utilization of SBRT may be increasing on a national level over more recent years, and therefore used a national database to investigate the patterns of care for the utilization of SBRT and CFRT for patients with locally-advanced unresectable pancreatic cancer, while also evaluating factors predictive of treatment decisions and observing survival outcomes.

Methods

Data source

De-identified data, exempt from IRB review, for patients with non-operative, non-metastatic, histologically confirmed pancreatic adenocarcinoma who either received CFRT (1.5–4.0 Gy per fraction to a dose of ≥45 Gy, n=11,879) or SBRT (6–15 Gy per fraction to a dose of ≥20 Gy, n=474) from 1998 to 2012 was taken from the National Cancer Database (NCDB). The NCDB, which includes greater than 1,500 Commission on Cancer accredited facilities and maintained by the American College of Surgeons and the American Cancer Society, is a national clinically oriented oncologic database encompassing more than 70% of newly diagnosed cancers in the United States (13).

Patient selection

Within the NCDB, 23,941 patients with unresectable, non-metastatic, histologically confirmed pancreatic adenocarcinoma treated with CFRT or SBRT were identified. While the NCDB does not define or describe particular factors leading to a patient's inability to undergo resection, typical criteria include solid tumor contact with superior mesenteric artery (SMA) or celiac artery >180°, contact with first jejunal SMA branch, aortic involvement, unreconstructible superior mesenteric vein (SMV) due to tumor involvement or occlusion, or contact with the most proximal draining jejunal branch into the SMV (14).

Definition of variables

SBRT was defined as ≥20 Gy at 6–15 Gy/fraction. CFRT was defined as ≥45 Gy at 1.5–4 Gy/fraction. Patients receiving <45 Gy of external beam radiation therapy (EBRT) were excluded to avoid inclusion of patients treated with palliative intent. Metropolitan, urban, and rural areas were defined using the 2013 U.S. Department of Agriculture Rural-Urban Continuum. "Metropolitans" were counties in metropolitan areas, "urban" areas were counties with an urban population of ≥2,500 but not in a metropolitan region, and "rural" areas were counties with an urban population of <2,500. Distance from residence to facility was measured using the treating facilities address and the center of the patient's zip code. Facility location was defined Northeast, South, Midwest, or West: Northeast: CT, MA, ME, NH, NJ, NY, PA, RI, VT; South: AL, AR, DC, DE, FL, GA, KY, LA, MD, MS, NC, OK, SC, TN, TX, VA,

WV; Midwest: IA, IL, IN, KS, MI, MN, MO, ND, NE, OH, SD, WI; West: AZ, AK, CA, CO, ID, HI, MT, NM, NV, OR, UT, WA, WY.

Statistical analysis

Data was analyzed using IBM SPSS, version 24.0 (IBM, Armonk, NY, USA). Univariate analysis was performed on all available factors potentially predictive for receipt of each given treatment modality. Univariate analysis was performed to identify significant factors ($P<0.05$) to be utilized in multivariable models. Propensity scores indicative of the likelihood of treatment utilization were generated from the significant variables ($P<0.05$) identified by the multivariable models to account for indication bias (15). A 1:1 nearest neighbor propensity matched cohort was generated. Balance among propensity matched cohorts was confirmed based on year of diagnosis, age, Charlson/Deyo score, race, insurance, residential setting, median income, high school degree, distant from residence to facility, facility type, facility location, case volume, T stage, nodal stage, primary location, chemotherapy, radiotherapy, and radiotherapy dose (all $P>0.10$).

Parsimonious multivariable survival analysis was performed for both the entire cohort and the propensity-match subset. Cox-Proportional Hazards modelling was used to formulate the multivariate section of survival analysis while log-rank statistics were used for the univariate analysis.

Results

Baseline characteristics

Baseline patient demographics and characteristics are given in *Table 1*. The median age was 68 years old, with an interquartile range (IQR) of 59–75 years old. Most patients were white (80%), lived in a metropolitan area (78%), had government insurance (59%), and had stage T4 (47%) disease. In the study cohort, patients predominantly received CFRT (97%) and of the total population, 50% received EBRT ≥45 Gy at 1.5–4 Gy/fraction. Eighty-nine percent (89%) also received chemotherapy. Patients treated with SBRT received from 6–12 Gy per fraction over 3–5 fractions for a total dose ranging from 24–40 Gy. The most common dose (Gy) per fraction in patients receiving SBRT were 8 (25.7%), 10 (18.8%), or 12 (16.5%). A majority of patients receiving SBRT were administered a dose of 30 Gy (24.9%), 24 Gy (24.1%), or 36 Gy (14.6%). Three and five were the

Table 1 Baseline characteristics of all patients with non-metastatic, unresectable pancreatic cancer who received EBRT or SBRT (n=23,941)

Baseline characteristics	Number of patients (%)
Sociodemographic factors	
Year of diagnosis	
1998–2001	5,215 (21.8)
2002–2005	5,952 (24.9)
2006–2009	7,100 (29.7)
2010–2012	5,674 (23.7)
Sex	
Male	12,029 (50.2)
Female	11,912 (49.8)
Age (years)	
<55	3,474 (14.5)
55–64	6,105 (25.5)
65–74	7,678 (32.1)
≥75	6,684 (27.9)
Charlson-Deyo comorbidity score	
0	12,516 (52.3)
1	3,769 (15.7)
≥2	1,049 (4.4)
Unknown	6,607 (27.6)
Race	
Non-Hispanic white	19,248 (80.4)
Hispanic white	788 (3.3)
Black	3,015 (12.6)
Other	655 (2.7)
Unknown	235 (1.0)
Insurance status	
Private	8,678 (36.2)
Government	14,106 (58.9)
None	565 (2.4)
Unknown	592 (2.5)
Residential setting	
Metropolitan	18,605 (77.7)
Urban	3,614 (15.1)
Rural	504 (2.1)
Unknown	1,218 (5.1)

Table 1 (*continued*)

Table 1 (*continued*)

Baseline characteristics	Number of patients (%)
Median income (residential area)	
<$38,000	4,281 (17.9)
$38,000–$47,999	5,769 (24.1)
$48,000–$62,999	6,223 (26.0)
≥$63,000	6,790 (28.4)
Unknown	878 (3.7)
% without high school degree (residential area)	
<7%	5,376 (22.5)
7–12.9%	7,815 (32.6)
13–20.9%	6,034 (25.2)
≥21%	3,845 (16.1)
Unknown	871 (3.6)
Distance from facility to residence (miles)	
<5	6,446 (26.9)
5–9.9	4,963 (20.7)
10–24.9	5,550 (23.2)
25+	6,138 (25.6)
Unknown	844 (3.5)
Facility type	
Community/comprehensive community	13,782 (57.6)
Academic/research	10,140 (42.4)
Unknown	19 (0.1)
Facility location	
Northeast	5,397 (22.5)
South	6,798 (28.4)
Midwest	8,586 (35.9)
West	3,160 (13.2)
Facility volume (cases)	
<20	5,792 (24.2)
21–40	6,304 (26.3)
41–80	5,113 (21.4)
>80	6,732 (28.1)

Table 1 (*continued*)

Baseline characteristics	Number of patients (%)
Pathological factors	
T stage	
1	734 (3.1)
2	3,277 (13.7)
3	6,897 (28.8)
4	11,280 (47.1)
X	1,753 (7.3)
Tumor size (cm)	
<3	4,763 (19.9)
3–4.9	9,743 (40.7)
≥5	3,923 (16.4)
Unknown	5,512 (23.0)
Nodal stage	
0	12,995 (54.3)
1	7,083 (29.6)
X	3,863 (16.1)
Primary location	
Head	16,008 (66.9)
Body	3,066 (12.8)
Tail	593 (2.5)
Other/NOS	4,274 (17.9)
Therapeutic factors	
Chemotherapy	
Yes	21,309 (89.0)
No	2,437 (10.2)
Unknown	195 (0.8)
Radiotherapy	
EBRT	23,245 (97.1)
SBRT	696 (2.9)
Radiotherapy dose	
SBRT ≥20 Gy at 6–15 Gy/fraction	474 (2.0)
EBRT <45 Gy at 1.5–4 Gy/fraction	2,672 (11.2)
EBRT ≥45 Gy at 1.5–4 Gy/fraction	11,879 (49.6)
Other/unknown	8,916 (37.2)

SBRT, stereotactic body radiotherapy; EBRT, external beam radiation therapy.

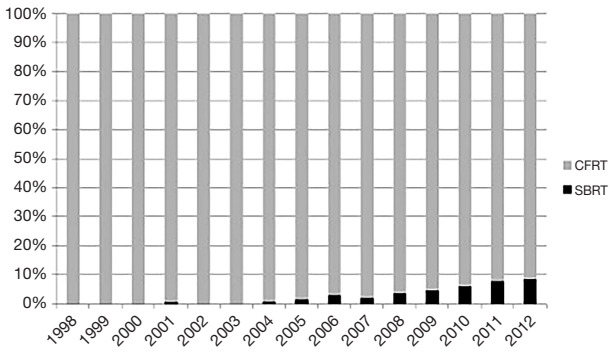


Figure 1 Utilization of SBRT and CFRT from 1998 to 2012 for individuals with locally-advanced pancreatic cancer. SBRT, stereotactic body radiotherapy; CFRT, conventionally fractionated radiotherapy.

most common number of fractions that patients receiving SBRT received, 65.2% and 28.5% respectively.

Trends in SBRT utilization

Utilization of SBRT increased from 0.2% to 7.4% (P<0.01) from 1998 to 2012 (*Figure 1*) with chemotherapy use remaining relatively constant at 89–91%. Patients receiving SBRT were less likely to receive chemotherapy than patients treated with CFRT (70.8% *vs.* 93.5%, P<0.05). SBRT patients receiving chemotherapy were started on chemotherapy greater than 1 week before radiation therapy (73.2% *vs.* 28.9%) and were less likely to begin chemotherapy the same week (4.5% *vs.* 59.9%) compared to patients receiving CFRT and chemotherapy.

Factors predictive of preferential SBRT utilization

Preferential use of SBRT over CFRT on multivariate analysis were later year of diagnosis, age ≥75 years, metropolitan residence, increased residential area income, increased distance from facility to residence, northeast facility location, increased facility volume, and no chemotherapy in the initial treatment plan (P<0.05). Exclusive to univariate analysis were lower T stage, smaller tumor size, and no nodal involvement for predicted utilization of SBRT (P<0.05). The factors most predictive of use were diagnosis >2010, facility volume >80 cases, and no prior chemo with 51, 7, and 6 odds ratios, respectively. These results are depicted in *Table 2*.

Survival outcomes

Median follow-up was 11.0 months (IQR: 7.2–17.0 months) and 18.4 months for survivors (IQR: 8.7–30.9 months). Unadjusted median overall survival (OS) for CFRT was 11.2 *vs.* 12.6 months for SBRT (P=0.002), depicted in *Figure 2*. Both the unadjusted multivariable model and the propensity-score matched multivariable model held this statistically significant OS advantage (HR =0.79, 95% CI: 0.70–0.91, P=0.001 and HR =0.79, 95% CI: 0.66–0.94, P=0.010, respectively). Multivariate analysis also showed factors that were associated with improved OS such as diagnosis after 2010, younger age, lower comorbidity score, white race, non-government insurance, higher residential area median income, facility location, facility volume, tumor size <3 cm, nodal stage zero, and receipt of chemotherapy (P<0.05). Results depicted in *Table 3*.

Discussion

In this analysis, we demonstrated an increased utilization of SBRT in patients with locally-advanced unresectable pancreatic cancer along with an associated small absolute OS benefit when compared with CFRT. Patients treated with SBRT saw an approximate OS benefit of 1.4 months compared to their CFRT treated counterparts, a finding consistent in the propensity matched model. Our analysis also exposed several positive prognostic factors for OS such as diagnosis after 2010, lower comorbidity score, younger age, tumor size <3 cm, nodal stage zero, and receipt of chemotherapy (P<0.05). Several of these factors have already been discussed in the literature (3,16-20).

Many groups have quantified OS in their studies evaluating SBRT, but we are unaware of any to date that have directly compared the survival outcomes of SBRT versus CFRT (6,9,12,21,22). The enhanced survival observed in our study might be explained by the high rates of LC (~72% at 1 year) afforded by dose escalation seen with SBRT (20,23,24). Improved LC is perhaps associated with better OS as LC addresses the modest portion of individuals who die specifically from local disease (25,26). It is important to highlight the improvement in OS favoring SBRT seen herein was observed despite a higher proportion of patients in the CFRT group receiving systemic therapy (70.8% *vs.* 93.5%).

To our knowledge, this report is also the first to utilize a national dataset to describe the increased utilizations of

Table 2 Comparative utilization of conventionally fractionated EBRT ≥45 Gy *vs.* SBRT ≥20 Gy at 6–15 Gy/fraction

Evaluated factors	EBRT (n=11,879), n (%)	SBRT (n=474), n (%)	Odds ratio	95% CI	P
Sociodemographic					
Year of diagnosis*					<0.0005
1998–2001	639 (99.8)	1 (0.2)	1	Reference	
2002–2005	2,931 (99.3)	20 (0.7)	4.36	0.58–32.5	
2006–2009	4,624 (96.7)	157 (3.3)	21.7	3.03–155	
2010–2012	3,685 (92.6)	296 (7.4)	51.3	7.19–366	
Sex					0.488
Male	6,032 (96.3)	233 (3.7)	1	Reference	
Female	5,847 (96.0)	241 (4.0)	1.07	0.89–1.28	
Age* (years)					<0.0005
<55	1,734 (96.8)	57 (3.2)	1	Reference	
55–64	3,221 (97.5)	82 (2.5)	0.77	0.55–1.09	
65–74	3,801 (97.0)	119 (3.0)	0.95	0.69–1.31	
≥75	3,123 (93.5)	216 (6.5)	2.10	1.56–2.83	
Charlson-Deyo comorbidity score					0.599
0	7,982 (95.8)	352 (4.2)	1	Reference	
1	2,403 (96.2)	94 (3.8)	0.89	0.70–1.12	
≥2	632 (95.9)	27 (4.1)	0.97	0.65–1.44	
Race					0.214
Non-Hispanic white	9,484 (96.1)	389 (3.9)	1	Reference	
Hispanic white	389 (95.8)	17 (4.2)	1.07	0.65–1.75	
Black	1,561 (97.0)	48 (3.0)	0.75	0.55–1.02	
Other	341 (97.2)	10 (2.8)	0.71	0.38–1.35	
Insurance status					0.023
Private	4,467 (96.7)	152 (3.3)	1	Reference	
Government	6,933 (95.7)	308 (4.3)	1.31	1.07–1.59	
None	286 (96.9)	9 (3.1)	0.92	0.47–1.83	
Residential setting*					0.001
Metropolitan	9,209 (96.0)	388 (4.0)	1	Reference	
Urban	1,842 (97.3)	51 (2.7)	0.66	0.49–0.88	
Rural	279 (99.3)	2 (0.7)	0.17	0.04–0.69	
Median income (residential area)*					<0.0005
<$38,000	2,078 (97.6)	51 (2.4)	1	Reference	
$38,000–$47,999	2,949 (96.6)	104 (3.4)	1.44	1.02–2.02	
$48,000–$62,999	3,191 (96.7)	109 (3.3)	1.39	0.99–1.95	
≥$63,000	3,290 (94.5)	191 (5.5)	2.37	1.73–3.24	

Table 2 (*continued*)

Table 2 (*continued*)

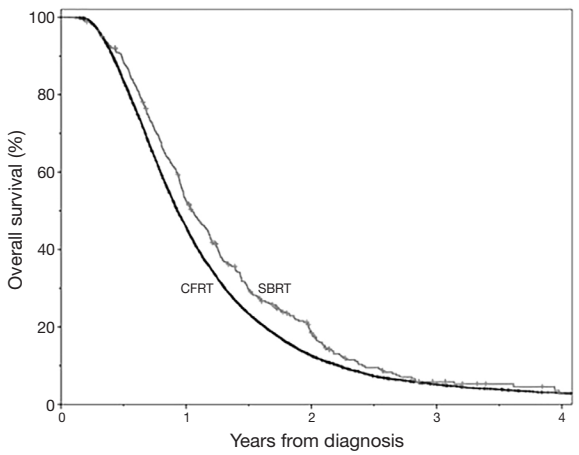
Evaluated factors	EBRT (n=11,879), n (%)	SBRT (n=474), n (%)	Odds ratio	95% CI	P
% without high school degree (residential area)					<0.0005
<7%	2,633 (94.3)	159 (5.7)	1	Reference	
7–12.9%	3,937 (96.2)	155 (3.8)	0.65	0.52–0.82	
13–20.9%	3,087 (97.2)	90 (2.8)	0.48	0.37–0.63	
≥21%	1,852 (97.3)	51 (2.7)	0.46	0.33–0.63	
Distance from facility to residence* (miles)					<0.0005
<5	3,219 (97.7)	77 (2.3)	1	Reference	
5–9.9	2,576 (96.7)	89 (3.3)	1.44	1.06–1.97	
10–24.9	2,846 (95.9)	121 (4.1)	1.78	1.33–2.38	
25+	2,875 (94.4)	170 (5.8)	2.47	1.88–3.25	
Facility type					<0.0005
Community/comprehensive	7,270 (97.7)	170 (2.3)	1	Reference	
Community academic/research	4,599 (93.8)	304 (6.2)	2.83	2.33-3.42	
Facility location*					<0.0005
Northeast	2,490 (93.0)	188 (7.0)	1	Reference	
South	3,401 (95.8)	150 (4.2)	0.58	0.47–0.73	
Midwest	4,342 (97.6)	105 (2.4)	0.32	0.25–0.41	
West	1,646 (98.2)	31 (1.8)	0.25	0.17–0.37	
Facility volume* (cases)					<0.0005
<20	2,993 (98.6)	42 (1.4)	1	Reference	
21–40	3,328 (98.3)	58 (1.7)	1.24	0.83–1.85	
41–80	2,657 (96.8)	89 (3.2)	2.39	1.65–3.46	
>80	2,901 (91.1)	285 (8.9)	7.00	5.04–9.72	
Pathological					
T stage					<0.0005
1	366 (92.9)	28 (7.1)	1	Reference	
2	1,598 (95.7)	72 (4.3)	0.59	0.38–0.92	
3	3,392 (95.3)	169 (4.7)	0.65	0.43–0.99	
4	5,869 (96.9)	186 (3.1)	0.41	0.27–0.62	
X	654 (97.2)	19 (2.8)	0.38	0.21–0.69	
Tumor size (cm)					<0.0005
<3	2,721 (94.4)	162 (5.6)	1	Reference	
3–4.9	5,222 (96.2)	206 (3.8)	0.66	0.54–0.82	
≥5	1,839 (96.9)	59 (3.1)	0.54	0.40–0.73	
Nodal stage					<0.0005
0	6,695 (95.6)	308 (4.4)	1	Reference	
1	3,666 (96.6)	130 (3.4)	0.77	0.63–0.95	
X	1,518 (97.7)	36 (2.3)	0.52	0.36–0.73	

Table 2 (*continued*)

Table 2 (*continued*)

Evaluated factors	EBRT (n=11,879), n (%)	SBRT (n=474), n (%)	Odds ratio	95% CI	P
Primary location					0.069
Head	7,954 (96.1)	326 (3.9)	1	Reference	
Body	1,594 (95.4)	76 (4.6)	1.16	0.90–1.50	
Tail	267 (97.1)	8 (2.9)	0.73	0.36–1.49	
Other/NOS	2,064 (97.0)	64 (3.0)	0.76	0.58–0.99	
Therapeutic					
Chemotherapy*					<0.0005
Yes	11,067 (97.1)	332 (2.9)	1	Reference	
No	764 (84.8)	137 (15.2)	5.98	4.84–7.39	

* indicates variable was significant on multivariable analysis and used to generate propensity score. SBRT, stereotactic body radiotherapy; EBRT, external beam radiation therapy; NOS, not otherwise specified.



Number at risk for Figure 2 pancreatic SBRT:

#At risk	Year 0	Year 1	Year 2	Year 3	Year 4
SBRT	364	187	54	12	3
CFRT	10,697	4,741	1,189	404	196

Figure 2 Unadjusted Kaplan-Meier survival analysis for treated with SBRT. SBRT, stereotactic body radiotherapy; CFRT, conventionally fractionated radiotherapy.

SBRT in treating patients with unresectable pancreatic cancer over the last decade. This trend is likely due to increased provider comfortability with the technique, the lack of clear benefit with CFRT, and the favorable toxicity profile. SBRT potentially offers other therapeutic benefits as well. For example, complications such as biliary or gastric obstruction, significant problems possibly experienced by patients, could be reduced with improved LC (27). Avoiding these complications would reasonably improve quality of life, and in fact, several studies have demonstrated a positive association between LC and quality of life in patients with locally-advanced pancreatic cancer (22,28). SBRT also offers a shorter treatment time which decreases stress on patients and families. Short treatment times also minimize interruptions in systemic therapy—important especially for a disease where the predominant pattern of failure is distant metastasis—and may even increase the ease of future integration of radiation with additional novel systemic therapies currently being explored such as CD40 agonists and immune checkpoint inhibitors (29,30).

We have also been the first to identify factors associated with preferential use of SBRT over CFRT: later year of diagnosis, age ≥75 years, metropolitan residence, increased residential area income, increased facility volume, no chemotherapy in the initial treatment plan, etc. The two strongest predictors in our analysis that pointed toward increased use of SBRT were diagnosis after 2010 and facility case volume. It is not surprising that use of SBRT steadily climbed from 1998 to 2012 as some of the first reports suggesting the benefit of SBRT were not published by the Stanford group until 2004. In fact, a 4.3-fold increase in the odds ratio illustrating increased utilization was seen from 1998–2001 to 2002–2005 alone. As more evidence was compiled depicting the rates of LC and OS, a further increase in the odds ratio was seen in 2006–2009 (27.1), ultimately culminating in a 51.3-fold increase in odds ratio in 2010–2012 compared to 1998–2001 (12,28,31). Increased pancreatic cancer volume at a given facility, specifically >80 cases, also served as a marker for increased preference for SBRT, although it was not as significant as year of diagnosis.

Table 3 Unadjusted multivariable Cox proportional hazard models for OS for patients who received conventionally fractionated EBRT ≥45 Gy or SBRT ≥20 Gy at 6–15 Gy/fraction

Significant factors	Hazard of death (95% CI)	P
Year of diagnosis		<0.0005
2002–2005	Reference	
2006–2009	1.00 (0.94–1.06)	
2010–2012	0.82 (0.77–0.88)	
Age (years)		0.003
<55	Reference	
55–64	1.01 (0.94–1.09)	
65–74	1.09 (1.00–1.18)	
≥75	1.16 (1.06–1.27)	
Comorbidity score		<0.0005
0	Reference	
1	1.11 (1.05–1.17)	
≥2	1.15 (1.04–1.27)	
Race		<0.0005
Non-Hispanic white	Reference	
Hispanic white	0.73 (0.63–0.84)	
Black	0.86 (0.80–0.93)	
Other	0.91 (0.79–1.06)	
Insurance status		0.009
Private	Reference	
Government	1.10 (1.03–1.18)	
None	1.10 (0.94–1.29)	
Median income (residential area)		<0.0005
<$38,000	Reference	
$38,000–$47,999	0.94 (0.87–1.01)	
$48,000–$62,999	0.93 (0.87–1.00)	
≥$63,000	0.83 (0.77–0.90)	
Facility location		0.003
Northeast	Reference	
South	1.13 (1.06–1.21)	
Midwest	1.10 (1.03–1.17)	
West	1.05 (0.96–1.14)	
Facility volume (cases)		0.029
<20	Reference	
21–40	1.08 (1.01–1.15)	
41–80	1.00 (0.94–1.07)	
>80	0.99 (0.92–1.05)	

Table 3 (*continued*)

Table 3 (*continued*)

Significant factors	Hazard of death (95% confidence)	P
Tumor size (cm)		<0.0005
<3	Reference	
3–4.9	1.15 (1.09–1.21)	
≥5	1.20 (1.12–1.29)	
Nodal stage		0.005
0	Reference	
1	1.07 (1.02–1.13)	
X	1.10 (1.02–1.19)	
Chemotherapy		<0.0005
No	Reference	
Yes	0.72 (0.65–0.79)	
Radiotherapy		0.001
EBRT ≥45 Gy at 1.5–4 Gy/fraction	Reference	
SBRT ≥20 Gy at 6–15 Gy/fraction	0.79 (0.70–0.91)	

SBRT, stereotactic body radiotherapy; EBRT, external beam radiation therapy.

Likely, institutions performing more cases, like academic institutions—another predictive factor for SBRT use—were more conformable with this new modality for treating non-operable pancreatic cancer.

Limitations of our study include those prevalent in many studies which extract data from large national databases: incomplete data, ascertainment bias, and coding error. Moreover, we were unable to collect toxicity data, LC, or disease free survival, as this information was not included in the NCDB. Many studies previously mentioned have commented on the toxicity profiles seen using SBRT. Most note mild but tolerable acute toxicities. However, in the past, there were concerns about significant rates of late bowel toxicity (≥ grade 2) as high as 47% seen in a study performed in 2008 (25 Gy/1 fx) where the importance of duodenal dose was not as well appreciated (11,12). More recent groups, though, have increased the fractionalization to as much as 5–6 fractions with close attention the duodenal dose constraints and have thus experienced much lower rates of late toxicity (<~10%) (6,22,28). Another limitation of this study is the unknown chemotherapy regimens received by the patients. The NCDB categorizes whether patients received chemotherapy but not which regimen they received, if they completed the course, etc. Thus we were unable to capture the potential impact for utilization of modern multi-agent chemotherapy regimens such as, FOLFIRINOX or Gemcitabine/Nab-Paclitaxel, which have dramatically improved OS relative to historical results for single agent chemotherapy such as was used in most trials comparing chemotherapy alone to chemotherapy plus radiation in locally-advanced pancreatic cancer (3,32,33). Of note, a number of ongoing studies are investigating the integration of SBRT and chemotherapy regimens such as FOLFIRINOX in locally-advanced (NCT01926197) and borderline resectable pancreatic cancer (ALLIANCE A021501). Lastly, our study does not address the cost effectiveness of SBRT versus CFRT. Studies have acknowledged that evaluating cost effectiveness is a difficult endeavor (34). However, at least one group was able to evaluate treatment cost effectiveness for locally advanced pancreatic cancer and found SBRT to be more cost effective that conventional radiotherapy and IMRT (35).

Conclusions

The use of SBRT has increased significantly from 1998 to 2012. Moreover, compared to CFRT, SBRT is associated with a small absolute improvement in OS. These findings, along with shorter treatment time, make SBRT an attractive option for patients with unresectable pancreatic cancer

warranting further research.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: De-identified data, exempt from IRB review, for patients with non-operative, non-metastatic, histologically confirmed pancreatic adenocarcinoma who either received CFRT or SBRT from 1998 to 2012 was taken from the National Cancer Database (NCDB).

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